# BIRTH DEFECT RISK FACTOR SERIES: DIAPHRAGMATIC HERNIA

## DEFINITION

Congenital diaphragmatic hernia occurs when the diaphragm is incompletely formed and the abdominal contents herniate into the chest. Infants with diaphragmatic hernia tend to have other additional birth defects, including chromosomal abnormalities (Forrester and Merz, 1998; Robert et al., 1997; Cannon et al., 1996; Howe et al., 1996; Langham et al., 1996; Torfs et al., 1992; Wenstrom et al., 1991; Adzick et al., 1985; David and Illingworth, 1976). Most diaphragmatic hernias occur on the left side of the body (Forrester and Merz, 1998; Robert et al., 1997; Howe et al., 1996; Torfs et al., 1992; Rasheed et al., 1992; Wenstrom et al., 1991; Adzick et al., 1985; David and Illingworth, 1976).

Diaphragmatic hernia can be detected prenatally with ultrasonography (Langham et al., 1996; Vintzileos et al., 1987). As a result, prenatal diagnosis and elective termination can reduce the birth prevalence of diaphragmatic hernia (Forrester and Merz, 1998; Riley et al., 1998; Cannon et al., 1996; Howe et al., 1996; Stoll et al., 1995; Juilian-Reynier et al., 1994; Stoll et al., 1992; Torfs et al., 1992; Adzick et al., 1985).

## EMBRYOLOGY

The diaphragm develops from four different structures: the septum transversum, pleuroperitoneal membranes, dorsal mesentary of the esophagus, and the body wall. The septum transversum is embryonic mesoderm that separates the pericardial (heart) cavity from the gastrointestinal system. The pleuro-peritoneal membranes separate the pleural (lung) and the peritoneal (abdominal) cavities. The dorsal mesentary of the esophagus is a layer of peritoneum. The septum transversum, pleuroperitoneal membranes, and dorsal mesentary of the esophagus fuse together by the sixth or seventh week of gestation to form the diaphragm. If the pleuroperitoneal membranes fail to fuse with the septum transversum and the dorsal mesentary of the esophagus by the tenth week of gestation, diaphragmatic hernia results. Diaphragmatic hernia is more common on the left side because the right pleuroperitoneal membrane usually fuses before the left pleuroperitoneal membrane because of the embryonic liver on the right side of the body.

## DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Several studies have investigated the relationship of **race/ethnicity** and risk for diaphragmatic hernia and failed to find any significant effect (Forrester and Merz, 1998; Robert et al., 1997; Langham; 1996; Torfs et al., 1992). However, one study did report diaphragmatic hernia to be more common among whites than nonwhites (Yang et al., 1994), and another reported the rate of diaphragmatic hernia to be higher in Europeans and South Asians than in Caribbeans (Leck and Lancashire, 1995).

**Secular trends** have been reported by several investigations (Forrester and Merz, 1998; Yang et al., 1994; Torfs et al., 1992). However, the trends were neither consistent nor statistically significant. One study observed **seasonal variation** in diaphragmatic hernia rates; however, this variation differed between types of diaphragmatic hernia (Torfs et al., 1992). Moreover, other investigations failed to identify any seasonal variation (Castilla et al., 1990; Bound et al., 1989).

Prevalence of diaphragmatic hernia shows variation by **geographic location**, with the rate being higher in rural than urban areas (Forrester and Merz, 1998; Torfs et al., 1992). One investigation failed to identify any association between diaphragmatic hernia and **altitude** (Castilla et al., 1999).

M**aternal age** does not appear to influence risk for diaphragmatic hernia (Forrester and Merz, 1998; Robert

et al., 1997; Torfs et al., 1992; David and Illingworth, 1976), although one study did report an increased risk with increased maternal age (Hollier et al., 2000). No clear association between diaphragmatic anomalies and **paternal age** has been identified (McIntosh et al., 1995). **Parity** does not affect diaphragmatic hernia rates (Robert et al., 1997; Torfs et al., 1992; David and Illingworth, 1976). The **recurrence risk** of a woman having another infant with diaphragmatic hernia has been reported to be 0.9-2% (Buyse, 1990).

**Infant sex** is associated with diaphragmatic hernia risk. Males were more likely than females to have the defect (Lary and Paulozzi, 2001; Robert et al., 1997; Yang et al., 1994; Torfs et al., 1992; Rasheed et al., 1992; Buyse, 1990; Rose-Spencer et al., 1981). Diaphragmatic hernia has been associated with lower **birth weight** and **intrauterine growth retardation** (Riley et al., 1998; Mili et al., 1991; Khoury et al., 1988). No association was found between anomalies of the diaphragm and **macrosomia** (Lapunzina et al., 2002; Waller et al., 2001). The literature on the relationship between diaphragmatic hernia and **multiple gestation pregnancy** has been inconsistent (Mastroiacovo; 1999; Riley et al., 1998; Robert et al., 1997; Torfs et al., 1992; Doyle et al., 1991; Kallen, 1986).

One investigation found no association between parental **consanguinity** and diaphragmatic hernia (Rittler et al., 2001).

## FACTORS IN LIFESTYLE OR ENVIRONMENT

Several investigations examined various maternal and environmental factors in relation to diaphragmatic hernia and found no increased risk for **maternal thyroid dysfunction** (**hyperthyroidism**, **hypothyroidism**) or **occupational and environmental chemicals** (Bos et al., 1994; Khoury et al., 1989). Studies have reported no association between **cephalosporin antibiotics**, **augmentin**, **ampicillin**, **calcium channel blockers**, or the **benzodiazepines** nitrazepam, medazepam, tofisopam, alprazolum, and clonazepam and anomalies of the diaphragm (Eros et al., 2002; Czeizel et al., 2001a; Czeizel et al., 2001b; Czeizel et al., 2001c; Sorensen et al., 2001). A **herbicide Nitrofen** has been found to induce diaphragmatic hernia in rats (Bos et al., 1994). Another study reported a higher than expected diaphragmatic hernia prevalence among infants whose mothers had **epilepsy**, although this increased risk may be associated with the **anticonvulsants** the mothers may have been taking (Bertollini et al., 1985).

An investigation failed to identify any significant association between diaphragmatic hernia and proximity to various types of **industry** (Castilla et al., 2000). One study observed no association between diaphragmatic hernia and **water chlorination** (Kallen and Robert, 2000).

No association between maternal **folic acid** use and diaphragmatic defects has been reported (Czeizel et al., 1996). Furthermore, a study that examined **co-trimoxazole**, a combination of trimethoprim and sulfamethoxazole that is a folic acid antagonist, failed to find any association between the medication and diaphragmatic anomalies (Czeizel, 1990).

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***Please Note:*** *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

*This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*